REMARKS

I. Claim status

Applicant has added claim 32, which reads on the elected invention. Upon entry of this amendment, claims 1-32 are pending; claims 1-4, 28, 29, and 32 are under examination and claims 5-27 and 30-31 are withdrawn.

Support for claim 32 can be found throughout the application as filed, including original claims 1 and 4. Accordingly, it does not add new matter and Applicant respectfully requests its entry.

II. Foreign Priority

The Examiner acknowledged that Applicant is entitled to a priority date of December 2, 2003 for the subject matter of claims 1-4.

III. Objections

The Examiner has withdrawn the previous objection to the specification and claim 2. The Office has maintained the objection to claim 28 for allegedly containing non-elected subject matter. Without acquiescence or disclaimer, Applicant will amend claim 28 as necessary at a later date, pending prosecution of the elected species.

IV. Withdrawn rejection

The Examiner has withdrawn the previous rejection under 35 U.S.C. § 102(e) of claim 29 over U.S. Patent Application Publication No. 2007/0105193 by Vilalta *et al.* (*Vilalta*).

V. Rejection under 35 U.S.C. § 102(a)

Claims 1, 28, and 29 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Marra *et al.*, *Science*, 300:1399-1404 (2003) (*Marra*) as evidenced by Genbank AY274119.3. According to the Office, *Marra* describes the protein of SARS-

CoV Tor 2 strain, "which has an amino acid sequence identical to the claimed S protein having the sequence of SEQ ID NO:3." Office Action at 4.

Applicant respectfully traverses. A claim is anticipated only if a single references teaches each and every limitation of the claims. *See* M.P.E.P. § 2131. *Marra* does not meet this standard.

Contrary to the Examiner's position, *Marra*, as evidenced by Genbank AY274119.3, does not report a sequence identical to SEQ ID NO:3, as shown by the attached sequence alignment[1]. The alignment shows, *inter alia*, a mismatch at about position 577 of SEQ ID NO:3 to the S-protein sequence allegedly reported in *Marra*. The mismatch is boxed for the Examiner's convenience. Thus, *Marra,* as evidenced by Genbank AY274119.3, does not teach a sequence identical to SEQ ID NO:3 and therefore does not anticipate claims 1, 28, and 29.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

VI. Rejections under 35 U.S.C. § 103(a)

A. Vilalta

Claims 2, 28, and 29 stand rejected under 35 U.S.C. § 103(a) over Vilalta. With the last Response, Applicant submitted a Declaration under 37 C.F.R § 1.132 by Dr. Nicolas Escriou establishing that Applicant had reduced the claimed invention to

[1] The alignment is of NCBI accession number AAP41037.1 to instant SEQ ID NO:3. The accession number cited in the Office Action, AY274119.3, is an approximately 29.7kb nucleotide sequence. Presently, AY274119.3 lists AAP41037.1 as the sequence corresponding to the S protein. Applicant provides this alignment solely to facilitate prosecution and in no way to suggest, agree, or acquiesce to any inherent suggestion by the office that AAP41037.1 was available before Applicant's priority date. In fact, the comments for accession AY274119.3 state "On Apr 30, 2003 this sequence version replaced gi:30088476." GI:30088476, in turn, is a 29736 bp sequence and includes no annotation of open reading frames and thus does not teach or suggest any specific coding sequence, let alone the claimed sequences.

practice before the earliest priority date of *Vilalta*. In the present Office Action, the Examiner avers that the declaration is insufficient to overcome *Vilalta* because "Applicants have not provided explicit description for the claimed S fragment consisting of 1-1193 until December 2, 2003, the filing date of France 0314151." Office Action at 6.

Applicant respectfully disagrees with the Office's conclusion. The *Escriou Declaration* establishes that Applicant had reduced the claimed invention to practice prior to May 16, 2003—the earliest priority date claimed by *Vilalta*. In particular, the *Escriou Declaration* establishes that Applicant had deposited two overlapping cDNA clones that encode the entire open reading frame of the SARS-CoV S protein with the Collection Nationale de Cultures de Microorganismes (CNCM) on May 12, 2003. *See also* paragraphs [0361]-[0363] and Table 1 of the published application. Based on the sequence of these deposits, the skilled artisan would recognize that Applicant was in possession of the claimed invention and could make and use it without undue experimentation, which is adequate to antedate *Vilalta*.

To further persuade the Office, Applicant also encloses the cover page and English language abstract of an invention report also dated May 12, 2003. The report explains that Applicant had achieved the cloning of sequences encoding the complete S protein by May 12, 2003. Furthermore, as stated in, *inter alia,* paragraph 75 and Table 1 of the published application, Applicant had deposited a cDNA encoding the complete S protein by June 20, 2003—which is earlier than the June 26, 2003 priority date of *Vilalta* asserted by the Office.

Accordingly, *Vilalta* is not prior art to this application for 35 U.S.C. § 103(a) purposes and this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Moreover, the present application also demonstrates that, quite by surprise, conventional prokaryotic (Example 2) and eukaryotic (Example 11) expression methods failed to efficiently produce isolated or purified S protein. For example, Example 2 describes experiments of production of S protein fragments in conventional prokaryotic systems. Example 2 describes producing a long version of S (SL, positions 14-1193 = ectodomain) and a short version of S (Sc, positions 475-1193 = fragment of ectodomain) in *Escherichia coli*. The SL was produced with low yield and was completely insoluble (figure 3), while the Sc was produced at a higher level but also exhibited a weak solubility. *See* paragraphs 434-435 of the published application. The Sc protein was purified by highly denaturing procedure (*see* paragraph 440 of the published application) and has a weak antigenic reactivity compared to the Nucleocapsid (N) recombinant protein (*see* paragraph 438 of the published application). Thus, prokaryotic expression is not adapted for producing an isolated S ectodomain polypeptide in a easy and high quantity manner.

Example 11 in the application, in turn, describes experiments in which Applicant found that nuclear transcription of S protein resulted in very low or undetectable yields in amounts of protein. The transcription was generally nuclear with the different plasmids (pCDNA, pCI, pTRIP) used in Example 11, because the S gene was under the control of the CMV promoter, which promotes a nuclear transcription. The expression level of S gene in these conventional eukaryotic expression systems is undetectable (in pCDNA plasmid) or weak (in pCI plasmid). *See* paragraph 604 of the published application. Expression yield was significantly increased by including splice sites (SD/SA) and Woodchuck Hepatitis Virus posttranscriptional regulatory element (WPRE) or constitutive transport element (CTE) sequences.

By developing means to produce substantial quantities of S proteins (*e.g.*, Ssol, an ectodomain fragment; *see* paragraph 614 of the published application), Applicant was able to develop an immunoassay (Example 13) as well as a vaccine composition (Example 14) that could elicit very high neutralizing antibody titers in mice. These high titers of neutralizing antibodies would be expected to provide protection against SARS-CoV infection. *See* paragraph 636 of the published application. Indeed, WO 2009/085025, which is enclosed for the Examiner's convenience, demonstrates that hamsters vaccinated with a Ssol-containing composition were fully protected against SARS CoV. *See, e.g.*, page 23, lines 19-22.

Applicant respectfully submits that the dramatic results described above rebut any *prima facie* obviousness rejection and illustrate that the skilled artisan would not have had a reasonable expectation of success in arriving at the claimed invention—absent the present application. *See* M.P.E.P. §§ 2141(V), 2142, 2143.02. Accordingly, the rejection should be withdrawn.

B. *Marra*

Claims 1-4, 28 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over *Marra* in view of Genbank AY274119.3. The Office acknowledges that *Marra* does not teach S polypeptides consisting of amino acids 1-1193, 14-1193, or 475-1193 of SEQ ID NO:3. Office Action at 7. However, the Office alleges that the prior art has provided a design need or market pressure to make immunogens and there are a finite number of predictable solutions for making the claimed S proteins, based on the amino acid sequence and structural characterization described in *Marra*. *Id.* at 8. The Office alleges that, based on *Marra*, one of ordinary skill in the art would

have made the claimed S proteins containing its ectodomain using routine molecular cloning and had a reasonable expectation of success. *Id.*

Applicant respectfully traverses and submits that the Office has not established *prima facie* obviousness for at least the reason that it has not provided a basis for which the skilled artisan would have modified the teachings of *Marra*—absent Applicant's disclosure. *See* M.P.E.P. § 2142 ("impermissible hindsight must be avoided and the legal conclusion [of obviousness] must be reached on the basis of the facts gleaned from the prior art"); § 2141.01(III)("[i]t is...necessary that the decisionmaker forget what he or she has been taught...about the claimed invention and cast the mind back to the time the invention was made.").

To establish *prima facie* obviousness, it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR Int'l Co. v. TeleFlex Inc.*, 127 S. Ct. 1727, 1741 (2007); *see also* In re Kahn, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)("[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."). Additionally, the number of possible combinations of elements described in the art is relevant to the obviousness inquiry, since "KSR requires the number of options to be 'small or easily traversed.'" *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 91 U.S.P.Q.2d 1569, 1573 (Fed. Cir. 2009), citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008) (compound found nonobvious where it was one of a large number of possibilities).

As discussed above, contrary to the Examiner's position, *Marra* does not disclose a Spike protein sequence identical to SEQ ID NO:3. *See* attached sequence alignment at about residue 577 of SEQ ID NO:3, which is boxed to highlight a mismatched residue for the Examiner's convenience. There are almost 24,000 different possible[2] single position substitutions in the 1255 residue full-length S-protein. Applicant submits that this number is too great to be easily traversed by the skilled artisan, as required by the courts, and thus, the Office's position that there are only a finite number of possible solutions to arrive at the claimed proteins is an improper rationale under which to support the present rejection. Therefore, as an initial matter, the Examiner has not provided any rationale to make this specific modification to the sequence taught in *Marra*.

The deficiency discussed above is compounded by the fact that, as acknowledged by the Office, *Marra* teaches that the ectodomain of S protein includes residues 1194-1195, in contrast to a terminus corresponding to residue 1193 of SEQ ID NO:3, as recited in claims 2-4. Additionally, *Marra* also fails to teach the specific sequences 1-1193, 14-1193, and 475-1193 recited in claims 2-4. Again, the Office's "finite number of predictable solutions" rationale does not support a legal conclusion of obviousness because the number of possible single-site substitutions, coupled with the number of possible truncations, is too numerous to be "easily traversed," as required by the courts. Thus, absent Applicant's disclosure, the skilled artisan would not have had any teaching or suggestion to modify the teachings of *Marra* to arrive at the claimed proteins.

---

[2] There are 19 possible substitutions at each of 1255 positions for a total of 19*155=23,845 possible single site substitutions.

Finally, as discussed under the previous rejection, the present application demonstrates that, quite by surprise, conventional expression methods did not efficiently produce adequate quantities of isolated or purified S protein. Applicant was able to achieve high levels of expression of an S protein and develop both diagnostic and vaccine compositions with dramatic results. Based on *Marra* and Genbank AY274119.3, the skilled artisan would not be able to achieve these same results with the necessary reasonable expectation of success, .

In short, *Marra* in view of Genbank AY274119.3 does not render the claimed proteins or polypeptides obvious and the rejection should be withdrawn.

CONCLUSION

The Examiner is encouraged to call the undersigned with any questions. Please grant any extensions of time required to enter this amendment and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 19, 2010

By: _____
Laurence A. Shumway, Ph.D.
Reg. No. 61,169
Phone: 617.452.1689

Attachments:

1) Sequence alignment
2) Partial invention report
3) WO 2009/085025